

Highlights:

- In Switzerland, incidence of childhood cancer increased by 18% from 1985-2014.
- Increase in incidence was mainly caused by brain tumours and leukaemias.
- Improved registration and diagnostics may have increased brain tumour incidence.
- Increasing trend for leukaemias may be real, but reasons remain elusive.

PRE-PRINT

FULL TITLE: Temporal trends in incidence of childhood cancer in Switzerland, 1985-2014

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1 **STRUCTURED ABSTRACT**

2 **Background:** Incidence of childhood cancer increased in most countries worldwide, but
 3 the reasons are unclear. This study investigates trends in childhood cancer incidence in
 4 Switzerland from 1985 to 2014.

5 **Methods:** We extracted data on all childhood cancer cases diagnosed at ages 0-14
 6 years in Switzerland from the Swiss Childhood Cancer Registry. We included ICC-3
 7 main groups I-XII and calculated age-standardised, cumulative, and age-specific
 8 incidence for different diagnostic groups. We analysed trends in annual age-
 9 standardised incidence using JoinPoint regression models.

10 **Results:** Over the study period from 1985-2014, 5104 of 5486 cancer diagnoses (93%)
 11 were microscopically verified. The proportion of children treated in paediatric cancer
 12 centres increased from 84% during 1985-1994 to 93% in 1995-2004 and 98% in 2005-
 13 2014 ($p < 0.001$). Using the 2010 European standard population, age-standardised
 14 incidence was 143 in 1985-1994, 154 in 1995-2004, and 162 per million in 2005-2014.
 15 Over the period 1985-2014, incidence for all cancers increased by 0.7% (95%
 16 confidence interval [CI] 0.5-1.0) per year, 0.8% (95% CI 0.2%-1.4%) for leukaemias,
 17 3.8% (95% CI 1.7%-6.0%) for epithelial neoplasms and melanomas, and 3.0% (95% CI
 18 1.3%-4.6%) for CNS tumours for the period 1985-2002.

19 **Conclusion:** Trends in incidence were driven mostly by increases among leukaemias
 20 and CNS tumours. For CNS tumours, observed trends may be explained at least
 21 partially by diagnostic changes and improved registration. For leukaemias, rising
 22 incidence may be real and at least partly due to changes in risk factors.

1 MAIN TEXT

2 Introduction

3 Incidence of childhood cancer during the decade 2001-2010 increased worldwide by
4 13% compared to rates in the 1980s.¹ The reasons for this increase remain unclear.
5 Improved case ascertainment and diagnostics could account for this trend,^{2,3} or the
6 trend could represent a real increase in cancer risks.⁴⁻⁸ Most countries have seen
7 increasing trends in childhood cancers, though results vary by reporting period and
8 cancer type.^{2,8-20} Switzerland is one of the few countries with a national childhood
9 cancer registry that has been in existence for over 40 years.²¹ However, registry data
10 on incidence of childhood cancer have only been published for the diagnostic period
11 1995-2005.^{22,23} Trends in the incidence of childhood cancer over the whole period
12 have not yet been analysed.

13 This study is the first to assess long-term trends in incidence of childhood cancer in
14 Switzerland. The two major aims are to calculate age-standardised, age-specific, and
15 cumulative incidence for three diagnostic periods—1985-1994, 1995-2004, and 2005-
16 2014—and to describe trends in age-standardised incidence over the entire period
17 from 1985 to 2014. We also assessed indices of quality of registered cases in the SCCR.

18 Methods

19 Study population and procedure

20 The Swiss Childhood Cancer Registry (SCCR) was founded by the Swiss Paediatric
21 Oncology Group (SPOG) in 1976 and initially registered patients included in clinical
22 trials.²¹ Beginning in 1981, all patients treated in paediatric cancer centres were
23 systematically included. In a retrospective study covering the period 1990-2004, we

discovered, however, that 16% of children with cancer had not been treated in paediatric cancer centres, including infants who were diagnosed only at autopsy in neonatal departments.²⁴

Between 2004 and 2007, the SCCR was reorganized according to international recommendations,^{25,26} and the review of diagnoses using pathology reports, quality indices, and retrospective inclusion of missed cases were introduced. Since then, the SCCR improved case completeness by comparing datasets with the population-based cancer registries of each Swiss canton, and by finding missed cases in mortality statistics.²⁷ The SCCR includes >95% of all childhood cancer cases diagnosed in Switzerland since 1995.

A clinical research coordinator in each paediatric cancer centre notifies the SCCR of new cases within two months of diagnosis. Children diagnosed with cancer before they reach the age of 16 years and older adolescents diagnosed with typical paediatric tumours are usually treated in paediatric cancer centres in Aarau, Basel, Bellinzona, Bern, Geneva, Lausanne, Lucerne, St. Gallen, and Zurich.

For this study, we included all children with Swiss residency at diagnosis who were registered in the SCCR and diagnosed with cancer according to one of the 12 main diagnostic groups of the ICC-3 at ages 0-14 years between 1 January 1985 and 31 December 2014.

1 **Measurements**

2 The SCCR registers patients with leukaemias and lymphomas, malignant and benign
3 CNS tumours, malignant solid tumours, and Langerhans cell histiocytosis who were
4 diagnosed at ages under 21 years in Switzerland. The registry records personal
5 information including name, sex, date of birth, address, nationality; diagnostic
6 information including exact diagnosis and its date, basis of diagnosis, site and grade of
7 primary and subsequent tumour(s), histological type and grade, immunophenotype
8 and genetics, stage at diagnosis, laterality, and site of any metastasis; and treatment
9 information that includes the name and type of treating institution, treatment type,
10 study type, and study protocol name. Diagnoses are classified according to the
11 International Classification of Diseases, tenth revision (ICD-10); topography and
12 morphology of the ICD for Oncology, third revision (ICD-O-3); and the International
13 Classification of Childhood Cancer, third edition (ICCC-3).^{25,28,29} The study was covered
14 by the Ethics Committee of the Canton of Bern approval to the SCCR (KEK-BE:
15 166/2014).

16 **Statistical methods**

17 We calculated incidence rates based on population data from the Swiss Federal
18 Statistical Office.³⁰ To assess indices of quality, we identified cancers treated in
19 paediatric cancer centres and cancers that had microscopically verified diagnoses that
20 were confirmed from histology of a primary tumour, haematological examination of
21 peripheral blood or bone marrow, or histology of metastasis. We then calculated the
22 average number of cases diagnosed per year and the proportional distribution of ICC-
23 3 main groups during the three decades 1985-1994, 1995-2004, and 2005-2014. We
24 calculated incidence rates (IR) for ICC-3 main groups and subgroups per decade

expressed per million children,²⁵ with direct standardization for age using the 2010 European standard population.³¹ We calculated cumulative IR, defined as the sum of age-specific IR over each year of age from 0 to 14 years and the risk of being diagnosed with cancer before the age of 15 (1 divided by the cumulative IR). We also computed age-specific IRs for the age groups <1, 1-4, 5-9, and 10-14 years. The 95% confidence intervals (95% CI) for the IR were calculated assuming Poisson distribution. We used R version 3.2.2 for data preparation, descriptive statistics, and calculation of IRs.

We examined trends in annual age-standardised incidence ratios from 1985 to 2014 for all diagnostic groups combined, separately for boys and girls, and for main diagnostic groups using JoinPoint, Version 4.0.2.2, assessing the magnitude and direction of trends over time and quantifying the average annual percentage change (AAPC).^{11,13,16,19,32-35} JoinPoint fitted straight regression lines through the data, with the natural logarithm of age-standardised incidence rates as dependent variable and calendar year (1985-2014) as independent variable. We used a maximum of two joinpoints to detect a maximum of three different trends, with a minimum of three years between joinpoints. We selected the trend lines that provided the best fit to observed age-standardised incidence rates based on the ratio of the sums of squared errors from the null model and the alternative model. Inference is conducted through Monte Carlo permutation tests as implemented in the software.³³

The study population included 98 patients (2%) who were registered from death certificate notifications. We had no information on ICC-3 main group for 12 of these and lacked dates of diagnosis for 75. We classified patients with missing diagnoses as having had other malignant neoplasms and imputed dates of diagnosis with the missforest package for R.³⁶ To generate the missing values we used observed data for year of birth, sex, cancer diagnosis, and age at death in the imputation model. We

- 1 excluded the 98 cases from all analyses using the specific subgroups of ICC-3 cancer
- 2 diagnoses (Supplemental Table 1).

3 **Results**

4 In 2014 Switzerland had a population of 7.825 million inhabitants, of which 1.225
5 million were 14 years old or younger. From 1985-2014, the SCCR registered 5486
6 cancer cases in children aged 0-14 years living in Switzerland (Supplemental Figure 1).
7 Of those, 5104 (93%) were microscopically verified (Table 1). The proportion of verified
8 cases of leukaemias has remained at 100% since 1995. Microscopic verification of
9 cancer was highest in 1995-2004 and then decreased again in 2005-2014. This was due
10 to decreases in CNS tumours, retinoblastomas, and renal tumours.

11 The proportion of cancers treated in paediatric cancer centres increased from 84%
12 during 1985-1994 to 98% for 2005-2014 (Supplemental Table 2). The increase was
13 largest for CNS tumours and epithelial neoplasms and melanomas; the proportion of
14 CNS tumours treated in paediatric cancer centres increased from 71% in 1985-1994 to
15 98% in 2005-2014.

16 During the decade 1985-1994, 1673 cancer cases were diagnosed at age 0-14 years;
17 1880 cases were diagnosed in 1995-2004, and 1933 cases in 2005-2014 (Table 1). In all
18 three decades, the most common cancers were leukaemias (31-34%), CNS tumours
19 (19-23%), and lymphomas (11-12%) (Table 2). The overall annual age-standardised
20 incidence rate per million children rose from 143 for 1985-1994 to 162 during 2005-
21 2014 (Table 2, Figure 1). Age-standardised incidence in all three decades was highest
22 for leukaemias, CNS tumours, and lymphomas, and the overall cumulative incidence
23 before the age of 14 years rose from 2135 to 2423 per million children from 1985-1994
24 to 2005-2014.

Childhood cancer was more common in boys than in girls, with a male to female ratio of 1.28 during 2005-2014 (Table 2). The male to female ratio was largest for Burkitt's lymphoma, 6.71, and smallest for thyroid carcinomas, 0.27 (Supplemental Table 1). Table 3 lists the age-specific incidences of childhood cancer over the period 2005-2014. Leukaemias and CNS tumours were among the most common cancers throughout all age group, neuroblastoma until 4 years, renal tumours from 1-4 years, and lymphoma from 5-14 years.

Overall, age-standardised childhood cancer incidence increased between 1985-2014 by 0.7% per year (95% CI 0.5%-1.0%), though trends differed between age groups, type of cancer, and sex (Table 4, Figure 2). This increase was highest for children diagnosed between the ages of 10 and 14 years. The annual increase of 0.8% (95% CI 0.2%-1.4%) from 1985-2014 for the incidence of leukaemias was mainly driven by a 1.2% (95% CI 0.4%-2.0%) increase among boys (Table 4). The incidence of CNS tumours increased annually by 3.0% (95% CI 1.3%-4.6%) from 1985-2002, but not thereafter (Table 4). Over the entire period, to 2014, the annual increase was 1.4% (95% CI 0.5%-2.4%) for boys and 1.7% (95% CI 0.7%-2.7%) for girls. Incidence of epithelial neoplasms and melanomas increased by 3.8% (95% CI 1.7%-6.0%) from 1985-2014, but because they account for only 3% of all cancer cases (165 of 5486 total cases) this had a very small effect on the overall trend (Tables 1 and 4).

1 Discussion

2 Overall childhood cancer incidence rates significantly increased between 1985-2014 in
3 Switzerland, mainly driven by leukaemias and CNS tumours. The trend for CNS
4 tumours plateaued in the 2000s, but continued for leukaemias and epithelial
5 neoplasms and melanomas. The increase in overall incidence rates was age-
6 dependent, with no increase in preschool children up to age 4, a slight increase in
7 children 5-9 years old, and a stronger increase in young adolescents 10-14 years old.

8 International comparison

9 The proportion of microscopically verified cases in the SCCR is high (>93%), suggesting
10 excellent validity of cancer diagnoses. This is comparable to validity ranging from 92-
11 98% reported in other European countries,^{17,37,12,1,38,11} and in Japan (90%),³⁹ the US
12 (95%),³² and Australia (97%).¹³ Lower proportions of microscopically verified cases in
13 certain tumours do not necessarily mean lower data quality, though. For
14 retinoblastoma, current treatment rarely involves surgical removal of the eye, which
15 has led to a decreasing proportion of microscopically verified cases from 41% for 1985-
16 1994 to 14% during 2005-2014. Patients with low-grade gliomas and certain high-grade
17 tumours are increasingly diagnosed with imaging techniques when surgical
18 intervention puts them at high risk for functional loss; many of these patients do not
19 undergo any surgery unless it becomes inevitable. The decreasing proportion of
20 microscopically verified CNS tumours, from 92% during 1985-1994 to 82% during 2005-
21 2014, reflects this.

22 Supplemental Table 3 compares the relative distribution of diagnostic groups and the
23 overall age-standardised incidence of childhood cancer in Switzerland to the Piedmont
24 region in Italy,¹¹ Spain,¹² Sweden,⁹ France,³⁷ Germany,³⁸ Austria,¹⁷ Western Europe

combined,¹ USA,⁴⁰ Canada,⁴¹ Australia,¹³ and Korea.¹⁴ The relative distribution of diagnostic groups was similar to these countries, but age-standardized leukaemia incidence was among the highest, with higher values observed in only Sweden, Germany, and Australia. The incidence of neuroblastoma was among the lowest, excepting only Sweden and Australia.

Overall cancer incidence rates in Switzerland continuously rose over the whole study period, from 1985-2014. Overall incidence rates increased in all world regions except sub-Saharan Africa from the 1980s to 2001-2010,¹ but have remained stable in Austria,¹⁷ Ireland,¹⁸ the USA,¹⁹ Canada,¹⁶ and Australia¹³ in more recent time periods (Supplemental Table 4). The increased incidence of childhood cancer observed in our study is mainly attributable to leukaemia and CNS tumours. Incidence of leukaemia increased steadily until 2014 without evidence of a plateau. Most countries also observed an increase,^{2,7-9,11-14,18,20} while studies from the USA and Austria reported stable leukaemia incidence (Supplemental Table 4).^{17,19,32} Leukaemia incidence in Canada first increased but levelled off after 1999.¹⁶ We observed that incidence of CNS tumours increased until 2002 and plateaued thereafter, similar to Australia.¹³ Many studies found increases over the entire study period,^{8,11,12,17,20} others found no increase,^{14,16,19,32,35,42,43} or even a decrease.³⁵ We also found that incidence of epithelial neoplasms and melanomas increased over the entire study period, similar to the USA,^{10,32} Australia,¹³ and Korea.¹⁴

Possible reasons for increasing trend in incidence

The increased incidence of childhood cancer may be attributable to several factors. First, improved case registration would increase the observed incidence. Patients with CNS tumours, with epithelial neoplasms and melanomas, and aged 10-14 years at time

of cancer diagnosis increasingly have been treated in paediatric oncology centres. These paediatric oncology centres collaborate closely with the SCCR and actively report every newly diagnosed child.²⁴ Since 1985, SCCR coverage has improved from 85% to 95%.²⁷ The SCCR has retrospectively registered missed cases, but we cannot exclude that some of the children with CNS tumours or children treated in earlier decades in adult facilities escaped registration, and thus that earlier incidence of childhood cancers is underestimated. Advances in medical diagnostics also may have increased apparent incidence rates. Imaging techniques have enhanced the capacity to diagnose otherwise undetected low-grade CNS tumours since the mid-1980s.^{2,44} Finally, medical and environmental risk factors could have increased the incidence of some cancers, including leukaemias in particular, which recently have increased in nearly all countries. Leukaemia and CNS tumours may be associated with exposure to low-level ionizing radiation,⁴⁵ which has likely increased in recent decades due to the increasing use of imaging techniques that rely upon ionizing radiation, especially computed tomography.⁴⁶ This might explain the age-dependent pattern of increase. Other potential risk factors include genetic causes, higher birth weight and parental age, increased infections, exposure to pesticides and traffic-related air pollution, as well as parental exposure to benzene.⁴⁷⁻⁴⁹ However, the results of this study do not allow us to draw conclusions about specific risk factors that may have contributed to the overall increasing incidence of cancer in general, and specifically of leukaemia and CNS tumours.

Strengths and limitations of the study

The nationwide, population-based coverage of the SCCR with a high completeness of registration is a real strength of this study.²⁷ Data quality was high with more than 90%

of the cases having been microscopically verified. We could include recent diagnostic years (until 2014) due to the fast reporting and quality control procedures in the SCCR.²¹ For the most recent years, the SCCR is in the process of exchanging data with the cantonal cancer registries. Therefore, we may have underestimated increases in incidence in the most recent period, although the SCCR missed very few cases in previous linkages. The sample size was limited by the comparatively small population of Switzerland, which led to wide confidence intervals for some diagnostic groups. Results should thus be interpreted cautiously because trends may reflect random fluctuations in incidence.

Conclusions

Changes in registration procedures and advances in medical diagnostics may explain the increase observed in the incidence in CNS tumours. For leukaemia, rising incidence may be real and due to changes in parental lifestyle, infections, pesticide exposure, air pollution, birth weight, or other risk factors. Future aetiological research should examine these long-term trends together with changes in medical and environmental risk factors.

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Table 1. Numbers of incident cancers and proportions of microscopically verified cancers among all children diagnosed with cancer in Switzerland at age 0-14 years from 1985-2014, by diagnostic period

	1985-1994				1995-2004				2005-2014				p-value ^b
	All cases	Microscopically verified ^a	%	95% CI	All cases	Microscopically verified ^a	%	95% CI	All cases	Microscopically verified ^a	%	95% CI	
<i>All cancers (N=5486)</i>	1673	1539	92.0	90.7; 93.3	1880	1769	94.1	93.0; 95.2	1933	1796	92.9	91.8; 94.1	0.047
<i>Age at diagnosis</i>													
0-4 years	804	727	90.4	88.4; 92.5	825	754	91.4	89.5; 93.3	830	755	91.0	89.0; 92.9	0.792
5-9 years	444	410	92.3	89.9; 94.8	498	475	95.4	93.5; 97.2	509	472	92.7	90.5; 95.0	0.112
10-14 years	425	402	94.6	92.4; 96.7	557	540	96.9	95.5; 98.4	594	569	95.8	94.2; 97.4	0.182
<i>ICCC-3 Main diagnostic group</i>													
I. Leukaemias	569	561	98.6	97.6; 99.6	581	581	100		647	647	100		<0.001
II. Lymphomas	201	200	99.5	98.5; 99.9	225	225	100		214	213	99.5	98.6; 99.9	0.580
III. CNS tumours	328	275	83.8	79.9; 87.8	429	376	87.6	84.5; 90.8	448	364	81.3	77.6; 84.9	0.033
IV. Neuroblastoma	134	117	87.3	81.7; 92.9	115	106	92.2	87.3; 97.1	119	112	94.1	89.9; 98.3	0.147
V. Retinoblastoma	46	19	41.3	27.1; 55.5	53	17	32.1	19.5; 44.6	42	6	14.3	3.7; 24.9	0.020
VI. Renal tumours	102	99	97.1	93.8; 99.9	98	97	99.0	97.0; 99.9	98	92	93.9	89.1; 98.6	0.135
VII. Hepatic tumours	18	12	66.7	44.9; 88.4	27	27	100		16	15	94	81.9; 99.9	0.002
VIII. Bone tumours	73	71	97	93.5; 99.9	95	95	100		79	79	100		0.091
IX. Soft tissue sarcomas	111	110	99	97.3; 99.9	129	128	99.2	97.7; 99.9	139	139	100		0.555
X. Germ cell tumours	45	42	93.3	86.0; 99.9	53	52	98.1	94.5; 99.9	57	56	98.2	94.8; 99.9	0.303
XI. Epithelial neoplasms & melanomas	31	29	93.5	84.9; 99.9	65	63	96.9	92.7; 99.9	69	69	100		0.140
XII. Other malignant neoplasms	15	4	26.7	4.3; 49.0	10	2	20.0	0.0; 44.8	5	4	80	44.9; 99.9	0.055

Abbreviations: CI, confidence interval; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, third edition.

^aIncludes histology of primary tumours and metastasis, and cytology; ^bp-value derived from Kruskal-Wallis rank sum test for trend, comparing the numbers of microscopically verified cases between the three time periods.

Table 2. Incidence of childhood cancer in Switzerland at age 0-14 years from 1985-2014, by diagnostic group and period

1985-1994					
	Average number of cases/year (%)	ASR per million population/year (95% CI) ^a	CR per million population (95% CI) ^b	1:N children ^c	Male/Female ^d
<i>All cancers</i>	166.6 (100)	143.1 (136.2; 150.0)	2135.3 (2108.8; 2161.8)	468	1.24
<i>ICCC-3 Main diagnostic group</i>					
I. Leukaemias	56.9 (34.2)	48.8 (44.8; 52.8)	730.3 (714.8; 745.8)	1369	1.29
II. Lymphomas	20.1 (12.1)	17.3 (14.9; 19.7)	259.2 (249.9; 268.4)	3858	2.14
III. CNS tumours	32.4 (19.4)	27.8 (24.8; 30.8)	417.1 (405.4; 428.8)	2398	1.17
IV. Neuroblastoma	13.4 (8.0)	11.5 (9.6; 13.5)	168.9 (161.4; 176.3)	5921	1.27
V. Retinoblastoma	4.6 (2.8)	4.0 (2.8; 5.1)	58.0 (53.6; 62.4)	17241	0.84
VI. Renal tumours	10.2 (6.1)	8.8 (7.1; 10.5)	129.8 (123.3; 136.4)	7704	0.76
VII. Hepatic tumours	1.8 (1.1)	1.6 (0.8; 2.3)	22.9 (20.1; 25.6)	43668	1.25
VIII. Bone tumours	7.3 (4.4)	6.3 (4.8; 7.7)	94.3 (88.7; 99.9)	10604	1.03
IX. Soft tissue sarcomas	10.9 (6.5)	9.4 (7.6; 11.1)	139.6 (132.8; 146.3)	7163	1.06
X. Germ cell tumours	4.4 (2.6)	3.8 (2.7; 4.9)	56.4 (52.1; 60.7)	17730	1.10
XI. Epithelial neoplasms & melanomas	3.1 (1.9)	2.7 (1.7; 3.6)	39.9 (36.3; 43.5)	25063	1.07
XII. Other malignant neoplasms	1.5 (0.9)	1.3 (0.6; 1.9)	19.1 (16.6; 21.6)	52356	0.88
1995-2004					
	Average number of cases/year (%)	ASR per million population/year (95% CI) ^a	CR per million population (95% CI) ^b	1:N children ^c	Male/Female ^d
<i>All cancers</i>	187.5 (100)	153.8 (146.8; 160.8)	2298.9 (2272.2; 2325.6)	435	1.27
<i>ICCC-3 Main diagnostic group</i>					
I. Leukaemias	57.8 (30.8)	47.4 (43.6; 51.3)	710.3 (695.4; 725.1)	1408	1.40
II. Lymphomas	22.5 (12.0)	18.1 (15.7; 20.4)	270.6 (261.4; 279.7)	3695	1.81
III. CNS tumours	42.9 (22.9)	34.8 (31.5; 38.1)	523.4 (510.6; 536.1)	1911	1.25
IV. Neuroblastoma	11.3 (6.0)	9.9 (8.0; 11.7)	144.6 (137.9; 151.3)	6916	0.92
V. Retinoblastoma	5.3 (2.8)	4.7 (3.4; 5.9)	68.4 (63.7; 73.0)	14620	0.96
VI. Renal tumours	9.8 (5.2)	8.2 (6.6; 9.9)	122.5 (116.3; 128.6)	8163	1.00
VII. Hepatic tumours	2.7 (1.4)	2.3 (1.4; 3.2)	33.9 (30.6; 37.1)	29499	3.50
VIII. Bone tumours	9.5 (5.1)	7.5 (6.0; 9.0)	112.8 (106.9; 118.7)	8865	0.94
IX. Soft tissue sarcomas	12.9 (6.9)	10.6 (8.7; 12.4)	157.7 (150.7; 164.7)	6341	1.48
X. Germ cell tumours	5.3 (2.8)	4.4 (3.2; 5.5)	65.1 (60.6; 69.5)	15361	0.77
XI. Epithelial neoplasms & melanomas	6.5 (3.5)	5.2 (3.9; 6.4)	77.5 (72.5; 82.4)	12903	0.81
XII. Other malignant neoplasms	1.0 (0.5)	0.8 (0.3; 1.4)	12.3 (10.4; 14.3)	81301	1.00
2005-2014					
	Average number of cases/year (%)	ASR per million population/year (95% CI) ^a	CR per million population (95% CI) ^b	1:N children ^c	Male/Female ^d
<i>All cancers</i>	192.4 (100)	162.3 (155.0; 169.5)	2423.4 (2395.5; 2451.2)	413	1.28
<i>ICCC-3 Main diagnostic group</i>					
I. Leukaemias	64.3 (33.4)	54.5 (50.3; 58.8)	816.0 (799.8; 832.2)	1225	1.57
II. Lymphomas	21.3 (11.1)	17.5 (15.2; 19.9)	262.4 (253.2; 271.5)	3811	1.77
III. CNS tumours	44.5 (23.1)	37.3 (33.9; 40.8)	560.7 (547.3; 574.1)	1783	1.17
IV. Neuroblastoma	11.9 (6.2)	10.5 (8.6; 12.3)	153.0 (146.0; 160.0)	6536	1.13
V. Retinoblastoma	4.2 (2.2)	3.7 (2.6; 4.8)	54.1 (49.9; 58.3)	18484	0.83
VI. Renal tumours	9.7 (5.0)	8.4 (6.7; 10.0)	124.4 (118.1; 130.7)	8039	0.80
VII. Hepatic tumours	1.6 (0.8)	1.4 (0.7; 2.1)	20.4 (17.9; 23.0)	49020	1.67
VIII. Bone tumours	7.9 (4.1)	6.5 (5.0; 7.9)	97.1 (91.5; 102.7)	10299	0.88
IX. Soft tissue sarcomas	13.9 (7.2)	11.6 (9.7; 13.6)	173.9 (166.5; 181.4)	5750	1.36
X. Germ cell tumours	5.7 (3.0)	4.8 (3.6; 6.1)	71.0 (66.2; 75.8)	14085	1.19
XI. Epithelial neoplasms & melanomas	6.9 (3.6)	5.6 (4.3; 7.0)	84.0 (78.8; 89.2)	11905	0.60
XII. Other malignant neoplasms	0.5 (0.3)	0.4 (0.1; 0.8)	6.3 (4.9; 7.7)	158730	1.50

Abbreviations: ASR, age-standardised incidence rate; CI, confidence interval; CNS, central nervous system; CR, cumulative incidence rate; ICC-3, International Classification of Childhood Cancer, third edition.

^aStandardised according to the 2010 European standard population; ^bCumulative incidence up to the age of 14 years; ^cNumber of children affected up to the age of 14 years in Switzerland; ^dmale:female ratio

Table 3. Age-specific incidence rate per million population in Switzerland and average cases per year from 2005-2014, by age at diagnosis and diagnostic group

	Age-specific incidence rate (95% CI)				Average cases per year per million population			
	<1 year	1-4 years	5-9 years	10-14 years	<1 year	1-4 years	5-9 years	10-14 years
<i>All cancers</i>	228.3 (195.9; 264.6)	209.5 (193.7; 226.3)	129.7 (118.6; 141.5)	142.0 (130.8; 154.0)	11.8	43.4	33.7	39.4
<i>ICCC-3 Main diagnostic group</i>								
I. Leukaemias	36.1 (24.0; 52.2)	99.1 (88.4; 110.8)	43.9 (37.6; 51.0)	32.7 (27.4; 38.7)	1.9	20.5	11.4	9.1
II. Lymphomas	3.9 (0.8; 11.3)	9.7 (6.5; 13.8)	14.9 (11.3; 19.3)	29.3 (24.4; 35.0)	0.2	2.0	3.9	8.1
III. CNS tumours	36.1 (24.0; 52.2)	38.3 (31.7; 45.8)	40.6 (34.5; 47.4)	33.6 (28.3; 39.7)	1.9	7.9	10.5	9.3
IV. Neuroblastoma	65.8 (49.0; 86.5)	18.7 (14.2; 24.1)	1.5 (0.6; 3.4)	1.0 (0.3; 2.5)	3.4	3.9	0.4	0.3
V. Retinoblastoma	25.8 (15.8; 39.8)	6.4 (3.9; 9.9)	0.5 (0.1; 1.9)	0.0 (0.0; 0.7)	1.3	1.3	0.1	0.0
VI. Renal tumours	18.1 (9.9; 30.3)	16.7 (12.5; 21.9)	6.4 (4.2; 9.5)	1.4 (0.5; 3.1)	0.9	3.5	1.7	0.4
VII. Hepatic tumours	7.7 (2.8; 16.8)	2.3 (0.9; 4.6)	0.5 (0.1; 1.9)	0.2 (0.0; 1.3)	0.4	0.5	0.1	0.1
VIII. Bone tumours	0.0 (0.0; 3.9)	1.6 (0.5; 3.8)	5.6 (3.5; 8.6)	12.5 (9.3; 16.4)	0.0	0.3	1.5	3.5
IX. Soft tissue sarcomas	11.6 (5.3; 22.0)	12.6 (8.9; 17.2)	9.2 (6.5; 12.8)	13.2 (10.0; 17.2)	0.6	2.6	2.4	3.7
X. Germ cell tumours	19.4 (10.8; 31.9)	3.5 (1.8; 6.3)	1.8 (0.7; 3.7)	5.8 (3.7; 8.6)	1.0	0.7	0.5	1.6
XI. Epithelial neoplasms & melanomas	1.3 (0.0; 7.2)	0.3 (0.0; 1.8)	4.4 (2.5; 7.0)	12.0 (8.9; 15.8)	0.1	0.1	1.1	3.3
XII. Other malignant neoplasms	2.6 (0.3; 9.3)	0.3 (0.0; 1.8)	0.3 (0.0; 1.4)	0.2 (0.0; 1.3)	0.1	0.1	0.1	0.1

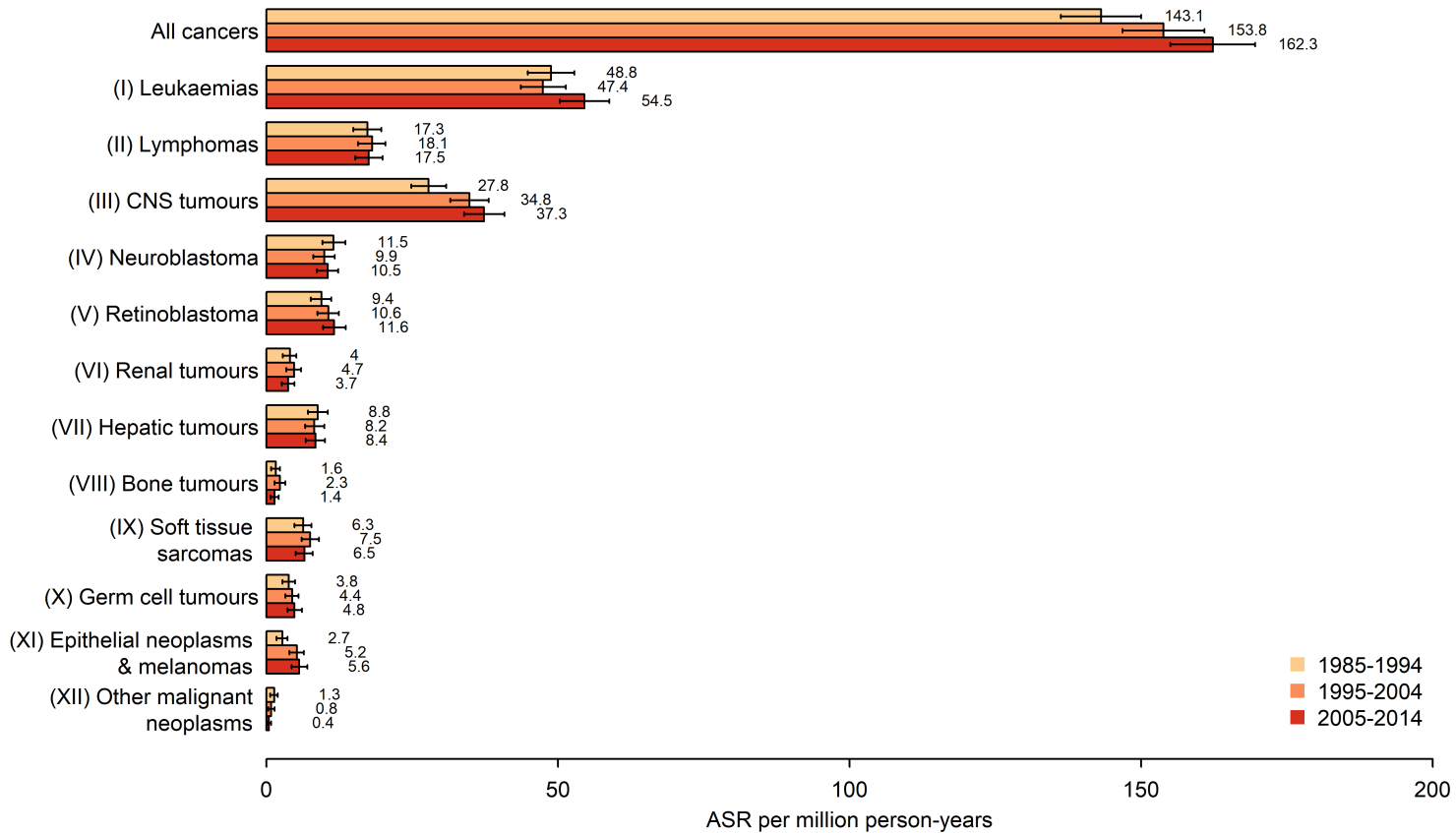
Abbreviations: CI, confidence interval; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, third edition.

Table 4. Average annual percentage change (AAPC) in incidence rates of childhood cancer by diagnostic group, age and sex in Switzerland 1985-2014: Results from JoinPoint regression.

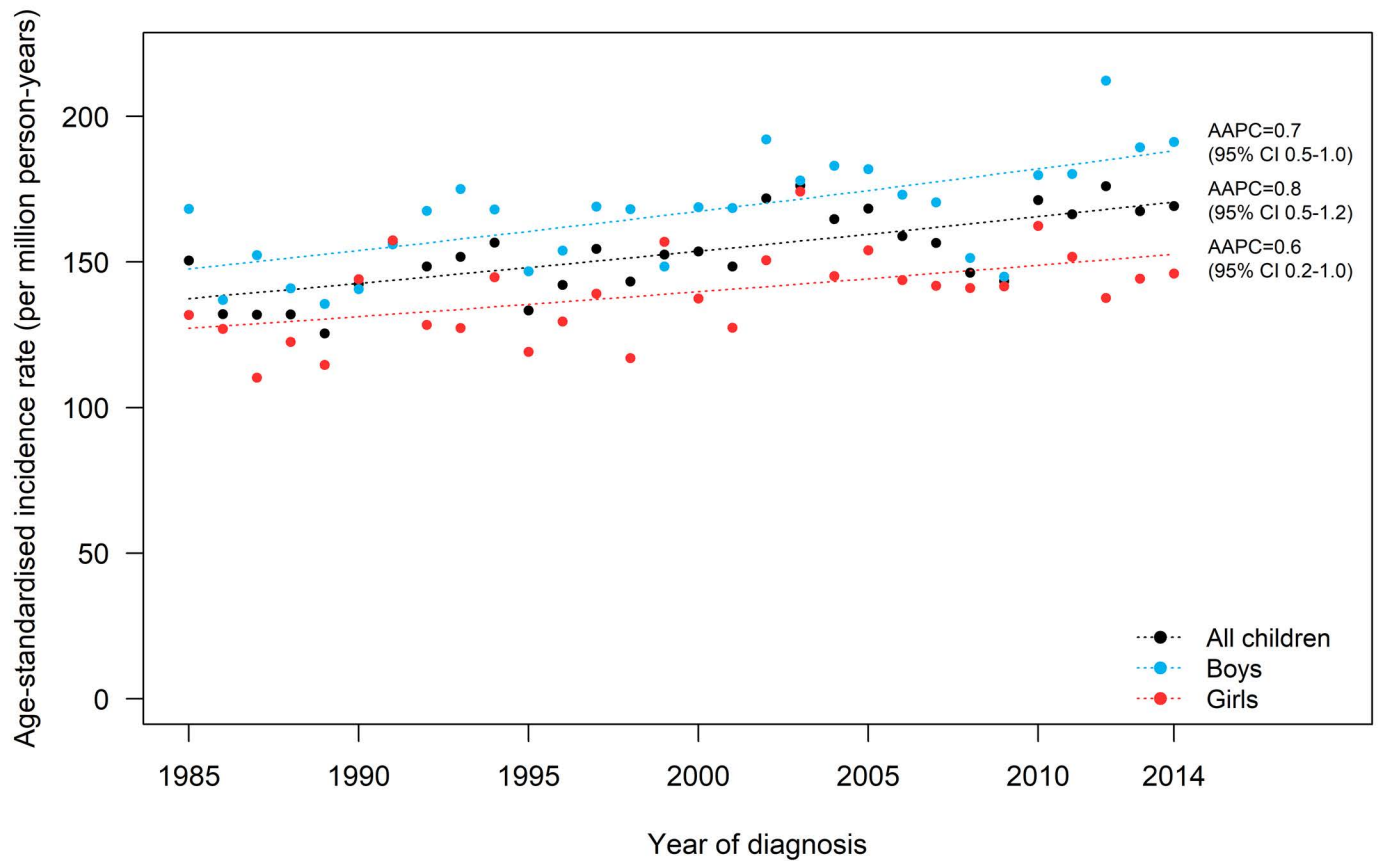
Diagnostic group	Trend 1		Trend 2	
	Period	AAPC (95% CI)	Period	AAPC (95% CI)
<i>All cancers</i>	1985-2014	0.7 (0.5; 1.0)		
0-4 years	1985-2014	0.3 (-0.1; 0.7)		
5-9 years	1985-2014	0.8 (0.2; 1.3)		
10-14 years	1985-2014	1.4 (0.9; 2.0)		
I. Leukaemias	1985-2009	0.8 (0.2; 1.4)		
II. Lymphomas	1985-2014	0.0 (-0.9; 1.0)		
III. CNS tumours	1985-2002	3.0 (1.3; 4.6)	2002-2014	-0.2 (-2.4; 2.1)
IV. Neuroblastoma	1985-2014	-0.5 (-1.7; 0.7)		
V. Retinoblastoma	1985-2014	-0.9 (-3.0; 1.2)		
VI. Renal tumours	1985-2014	-0.3 (-1.5; 0.9)		
VII. Hepatic tumours	1985-2014	n.a.		
VIII. Bone tumours	1985-2014	0.2 (-0.9; 1.4)		
IX. Soft tissue sarcomas	1985-2014	1.0 (-0.4; 2.5)		
X. Germ cell tumours	1985-2014	1.6 (-0.2; 3.4)		
XI. Epithelial neoplasms & melanomas	1985-2014	3.8 (1.7; 6.0)		
XII. Other malignant neoplasms	1985-2014	n.a.		
<i>Boys</i>				
All cases	1985-2014	0.8 (0.5; 1.2)		
I. Leukaemias	1985-2010	1.2 (0.4; 2.0)		
II. Lymphomas	1985-2014	0.0 (-1.1; 1.0)		
III. CNS tumours	1985-2014	1.4 (0.5; 2.4)		
IV. Neuroblastoma	1985-2014	-1.1 (-2.3; 0.1)		
V. Retinoblastoma	1985-2014	n.a.		
VI. Renal tumours	1985-2014	0.1 (-1.9; 2.1)		
VII. Hepatic tumours	1985-2014	n.a.		
VIII. Bone tumours	1985-2014	n.a.		
IX. Soft tissue sarcomas	1985-2014	0.7 (-0.8; 2.2)		
X. Germ cell tumours	1985-2014	n.a.		
XI. Epithelial neoplasms & melanomas	1985-2014	n.a.		
XII. Other malignant neoplasms	1985-2014	n.a.		
<i>Girls</i>				
All cases	1985-2014	0.6 (0.2; 1.0)		
I. Leukaemias	1985-2014	0.2 (-0.6; 0.9)		
II. Lymphomas	1985-2014	0.1 (-1.8; 2.0)		
III. CNS tumours	1985-2014	1.7 (0.7; 2.7)		
IV. Neuroblastoma	1985-2014	0.6 (-1.3; 2.6)		
V. Retinoblastoma	1985-2014	n.a.		
VI. Renal tumours	1985-2014	-0.7 (-2.4; 1.1)		
VII. Hepatic tumours	1985-2014	n.a.		
VIII. Bone tumours	1985-2014	0.7 (-0.9; 2.5)		
IX. Soft tissue sarcomas	1985-2014	n.a.		
X. Germ cell tumours	1985-2014	n.a.		
XI. Epithelial neoplasms & melanomas	1985-2014	n.a.		
XII. Other malignant neoplasms	1985-2014	n.a.		

Abbreviations: AAPC, average annual percentage change; CI, confidence interval; CNS, central nervous system; n.a., not applicable.

Bold letters indicate AAPCs with p-values<0.05.



A) All cancer diagnoses



B) Leukaemias

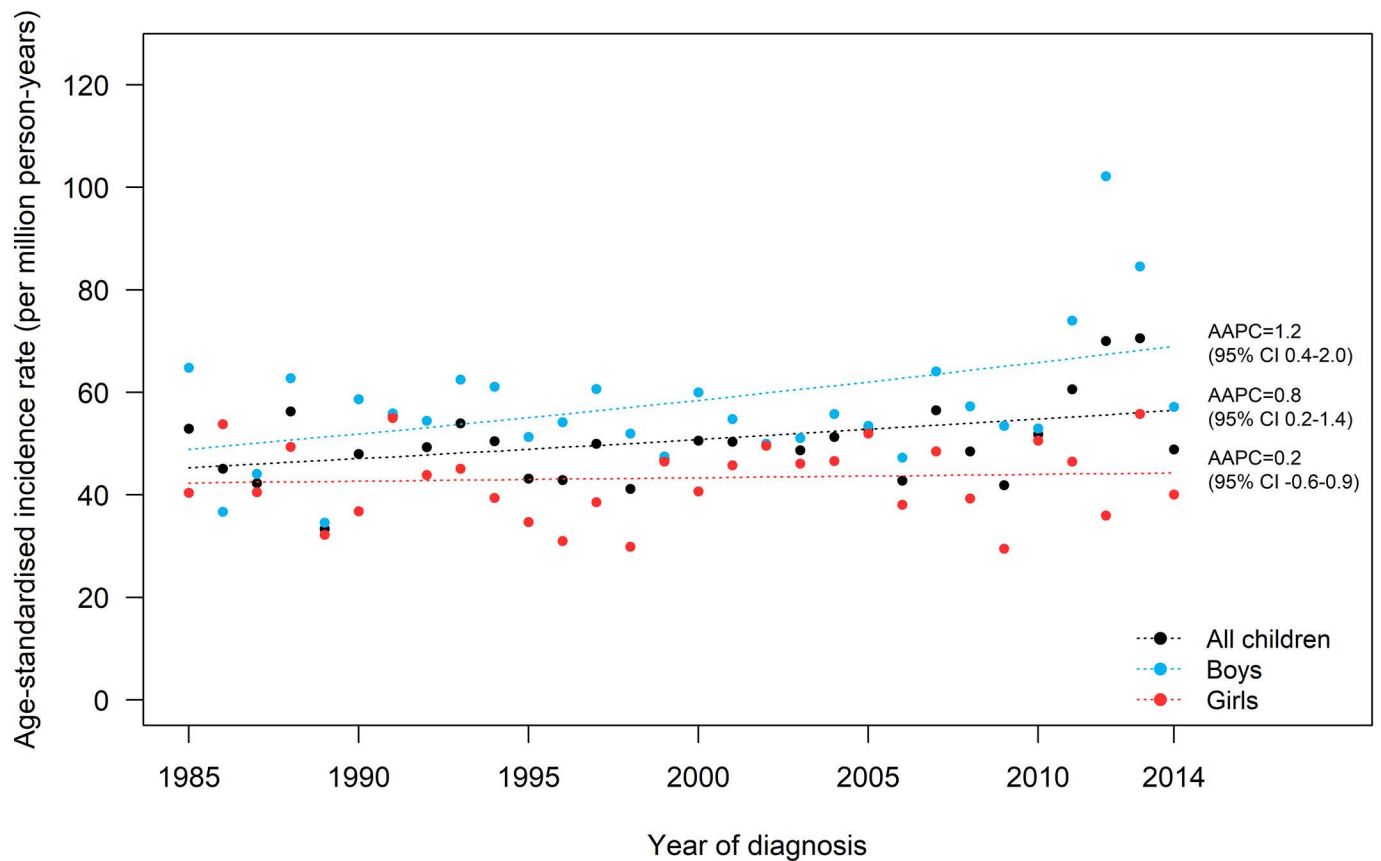


Figure legends

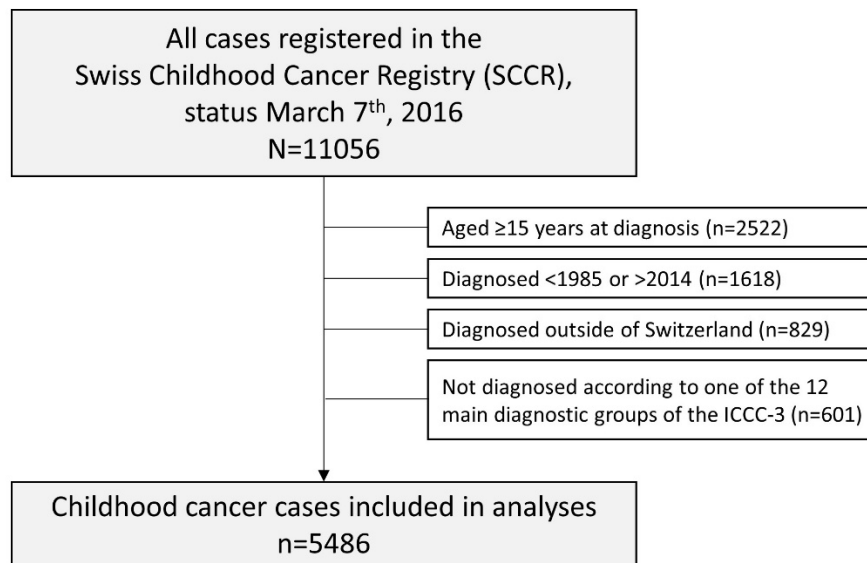
Figure 1. Comparison of incidence of childhood cancer between 1985-1994, 1995-2004 and 2005-2014, by cancer diagnosis.

Abbreviations: ASR, Age-standardized incidence rate.

Cancer diagnoses were classified according to the International Classification of Childhood Cancer, third edition (ICCC-3). Incidence rates were age-standardized according to the 2010 European standard population. Error bars show 95% confidence intervals.

Figure 2. Trends in incidence rates (per million person-years) in Switzerland between 1985 and 2014, standardized according to the 2010 European standard population, for A) all childhood cancer diagnoses combined and B) leukaemias. Trends were modelled using Joinpoint regression.

Abbreviations: AAPC, average annual percentage change; CI, confidence interval.



Supplemental Figure 1. Flow diagram from the number of registered cases in the SCCR to those eligible for the study.

Abbreviations: ICC-3, International Classification of Childhood Cancer, third edition.

Supplemental Table 1a. Incidence of childhood cancer in Switzerland at age 0-14 years from 2005-2014, by main diagnostic group and subgroup*

Diagnostic group/subgroup	Average number of cases/year (%)	ASR per million population/year (95% CI) ^a	CR per million population (95% CI) ^b	1:N children ^c	Male/Female ^d
<i>All cancers</i>	191.4 (100)	161.4 (154.2; 168.7)	2410.6 (2382.8; 2438.4)	415	1.28
I. Leukaemias	64.3 (33.6)	54.5 (50.3; 58.8)	816.0 (799.8; 832.2)	1225	1.57
a. Lymphoid leukaemias	51.7 (27.0)	43.9 (40.1; 47.7)	657.3 (642.8; 671.9)	1521	1.47
b. Acute myeloid leukaemias	7.8 (4.1)	6.6 (5.1; 8.1)	98.4 (92.8; 104.0)	10163	1.89
c. Chronic myeloproliferative diseases	0.9 (0.5)	0.7 (0.3; 1.2)	11.1 (9.2; 13.0)	90090	3.50
d. Myelodysplastic syndrome and other myeloproliferative diseases	3.2 (1.7)	2.7 (1.8; 3.6)	40.3 (36.7; 43.9)	24814	3.00
e. Unspecified and other specified leukaemias	0.7 (0.4)	0.6 (0.2; 1.0)	8.9 (7.2; 10.6)	112360	0.75
II. Lymphomas	21.2 (11.1)	17.5 (15.1; 19.8)	261.1 (251.9; 270.2)	3830	1.75
a. Hodgkin lymphomas	9.6 (5.0)	7.8 (6.2; 9.3)	115.7 (109.6; 121.8)	8643	0.88
b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	5.7 (3.0)	4.7 (3.5; 6.0)	71.0 (66.2; 75.8)	14085	2.80
c. Burkitt lymphoma	5.4 (2.8)	4.5 (3.3; 5.7)	68.0 (63.3; 72.6)	14706	6.71
d. Miscellaneous lymphoreticular neoplasms	0.5 (0.3)	0.4 (0.1; 0.8)	6.4 (5.0; 7.9)	156250	0.25
III. CNS tumours	43.9 (22.9)	36.8 (33.4; 40.3)	553.0 (539.7; 566.4)	1808	1.17
a. Ependymomas and choroid plexus tumour	4.8 (2.5)	4.1 (3.0; 5.3)	61.1 (56.7; 65.6)	16367	1.29
b. Astrocytomas	18.4 (9.6)	15.4 (13.1; 17.6)	231.2 (222.6; 239.8)	4325	1.07
c. Intracranial and intraspinal embryonal tumours	8.0 (4.2)	6.8 (5.3; 8.2)	101.8 (96.1; 107.5)	9823	1.35
d. Other gliomas	5.1 (2.7)	4.3 (3.1; 5.5)	64.9 (60.4; 69.5)	15408	1.32
e. Other specified intracranial and intraspinal neoplasms	6.7 (3.5)	5.5 (4.2; 6.8)	82.8 (77.6; 87.9)	12077	1.16
f. Unspecified intracranial and intraspinal neoplasms	0.9 (0.5)	0.8 (0.3; 1.2)	11.2 (9.3; 13.1)	89286	0.80
IV. Neuroblastoma	11.8 (6.2)	10.4 (8.5; 12.2)	151.7 (144.7; 158.7)	6592	1.11
a. Neuroblastoma and ganglioneuroblastoma	11.8 (6.2)	10.4 (8.5; 12.2)	151.7 (144.7; 158.7)	6592	1.11
b. Other peripheral nervous cell tumour	0				
V. Retinoblastoma	4.2 (2.2)	3.7 (2.6; 4.8)	54.1 (49.9; 58.3)	18484	0.83
VI. Renal tumours	9.7 (5.1)	8.4 (6.7; 10.0)	124.4 (118.1; 130.7)	8039	0.80
a. Nephroblastoma and other nonepithelial renal tumours	9.2 (4.8)	7.9 (6.3; 9.6)	118.3 (112.1; 124.5)	8453	0.80
b. Renal carcinomas	0.5 (0.3)	0.4 (0.1; 0.8)	6.1 (4.7; 7.5)	163934	0.67
c. Unspecified renal tumours	0				
VII. Hepatic tumours	1.5 (0.8)	1.3 (0.6; 2.0)	19.1 (16.7; 21.6)	52356	2.00
a. Hepatoblastoma	1.4 (0.7)	1.2 (0.6; 1.9)	18.0 (15.6; 20.4)	55556	1.80
b. Hepatic carcinomas	0.1 (0.1)	0.1 (0.0; 0.2)	1.2 (0.5; 1.8)	833333	n.a.
c. Unspecified hepatic tumours	0				

Supplemental Table 1b (continued). Incidence of childhood cancer in Switzerland at age 0-14 years from 2005-2014, by main diagnostic group and subgroup*

Diagnostic group/ subgroup	Average number of cases/year (%)	ASR per million population/year (95% CI) ^a	CR per million population (95% CI) ^b	1:N children ^c	Male/Female ^d
VIII. Bone tumours	7.9 (4.1)	6.5 (5.0; 7.9)	97.1 (91.5; 102.7)	10299	0.88
a. Osteosarcomas	3.8 (2.0)	3.1 (2.1; 4.1)	46.6 (42.7; 50.4)	21459	0.90
b. Chondrosarcomas	0.1 (0.1)	0.1 (-0.1; 0.2)	1.2 (0.5; 1.8)	833333	n.a.
c. Ewing tumour and related sarcomas of bone	3.9 (2.0)	3.2 (2.2; 4.2)	48.2 (44.3; 52.2)	20747	0.95
d. Other specified bone tumours	0				
e. Unspecified malignant bone tumours	0.1 (0.1)	0.1 (0.0; 0.2)	1.2 (0.5; 1.8)	833333	n.a.
IX. Soft tissue sarcomas	13.9 (7.3)	11.6 (9.7; 13.6)	173.9 (166.5; 181.4)	5750	1.36
a. Rhabdomyosarcomas	7.8 (4.1)	6.6 (5.1; 8.1)	98.5 (92.9; 104.1)	10152	1.36
b. Fibrosarcomas, peripheral nerve sheath tumours, other fibrous neoplasms	1.0 (0.5)	0.8 (0.3; 1.3)	12.3 (10.3; 14.3)	81301	2.33
c. Kaposi sarcoma	0				
d. Other specified soft tissue sarcomas	4.0 (2.1)	3.3 (2.3; 4.3)	49.4 (45.4; 53.4)	20243	0.90
e. Unspecified soft tissue sarcomas	1.1 (0.6)	0.9 (0.4; 1.5)	13.8 (11.7; 15.9)	72464	4.50
X. Germ cell tumours	5.7 (3.0)	4.8 (3.6; 6.1)	71.0 (66.2; 75.8)	14085	1.19
a. Intracranial and intraspinal germ cell tumours	1.5 (0.8)	1.2 (0.6; 1.9)	18.5 (16.1; 21.0)	54054	2.00
b. Malignant extracranial and extragonadal germ cell tumours	1.7 (0.9)	1.5 (0.8; 2.2)	21.9 (19.2; 24.5)	45662	0.70
c. Malignant gonadal germ cell tumours	2.4 (1.3)	2.0 (1.2; 2.8)	29.3 (26.3; 32.4)	34130	1.18
d. Gonadal carcinomas	0				
e. Other and unspecified malignant gonadal tumours	0.1 (0.1)	0.1 (0.0; 0.3)	1.3 (0.6; 1.9)	769231	n.a.
XI. Epithelial neoplasms & melanomas	6.9 (3.6)	5.6 (4.3; 7.0)	84.0 (78.8; 89.2)	11905	0.60
a. Adrenocortical carcinomas	0.2 (0.1)	0.2 (0.0; 0.4)	2.5 (1.6; 3.4)	400000	1.00
b. Thyroid carcinomas	1.4 (0.7)	1.1 (0.5; 1.7)	16.8 (14.5; 19.1)	59524	0.27
c. Nasopharyngeal carcinomas	0.2 (0.1)	0.2 (0.0; 0.4)	2.4 (1.5; 3.2)	416667	1.00
d. Malignant melanomas	1.5 (0.8)	1.2 (0.6; 1.9)	18.5 (16.0; 20.9)	54054	0.50
e. Skin carcinomas	0.6 (0.3)	0.5 (0.1; 0.9)	7.5 (6.0; 9.1)	133333	2.00
f. Other and unspecified carcinomas	3.1 (1.6)	2.5 (1.6; 3.4)	37.5 (34.1; 41.0)	26667	0.63
XII. Other malignant neoplasms	0.4 (0.2)	0.3 (0.0; 0.7)	5.0 (3.8; 6.3)	200000	n.a.
a. Other specified malignant tumours	0.2 (0.1)	0.2 (0.0; 0.4)	2.6 (1.7; 3.5)	384615	1.00
b. Other unspecified malignant tumours	0.1 (0.1)	0.1 (0.0; 0.3)	1.3 (0.6; 1.9)	769231	n.a.

Abbreviations: ASR, age-standardised incidence rate; CI, confidence interval; CNS, central nervous system; CR, cumulative incidence rate.

* Analyses exclude 98 cases from death certificate notifications because data on specific diagnostic subgroups was not available.

^a Standardised according to the 2010 European standard population; ^b Cumulative incidence up to the age of 14 years; ^c Number of children affected up to the age of 14 years in Switzerland; ^d male:female ratio.

Supplemental Table 2. Proportions of patients treated in paediatric cancer centres^a among all children diagnosed with cancer in Switzerland at age 0-14 years from 1985-2014, by diagnostic period

	1985-1994				1995-2004				2005-2014				p-value ^b
	All cases	Paediatric cancer centres ^a	%	95% CI	All cases	Paediatric cancer centres ^a	%	95% CI	All cases	Paediatric cancer centres ^a	%	95% CI	
<i>All cancers (N=5486)</i>	1673	1407	84.1	82.3; 85.9	1880	1748	93.0	91.8; 94.1	1933	1891	97.8	97.2; 98.5	<0.001
<i>Age at diagnosis</i>													
0-4 years	804	689	85.7	83.3; 88.1	825	791	95.9	94.5; 97.2	830	818	98.6	97.7; 99.4	<0.001
5-9 years	444	372	83.8	80.4; 87.2	498	469	94.2	92.1; 96.2	509	496	97.4	96.1; 98.8	<0.001
10-14 years	425	346	81.4	77.7; 85.1	557	488	87.6	84.9; 90.3	594	577	97.1	95.8; 98.5	<0.001
<i>ICCC-3 Main diagnostic group</i>													
I. Leukaemias	569	518	91.0	88.7; 93.4	581	567	97.6	96.3; 98.8	647	644	100	99.0; 99.9	<0.001
II. Lymphomas	201	179	89.1	84.7; 93.4	225	213	94.7	91.7; 97.6	214	211	98.6	97.0; 99.9	<0.001
III. CNS tumours	328	234	71.3	66.4; 76.2	429	390	90.9	88.2; 93.6	448	437	97.5	96.1; 99.0	<0.001
IV. Neuroblastoma	134	117	87.3	81.7; 92.9	115	113	98.3	95.9; 99.9	119	118	99	97.5; 99.9	<0.001
V. Retinoblastoma	46	41	89.1	80.1; 98.1	53	49	92.5	85.3; 99.6	42	40	95.2	88.8; 99.9	0.566
VI. Renal tumours	102	99	97.1	93.8; 99.9	98	97	99.0	97.0; 99.9	98	98	100		0.186
VII. Hepatic tumours	18	11	61.1	38.6; 83.6	27	27	100		16	15	94	81.9; 99.9	<0.001
VIII. Bone tumours	73	63	86.3	78.4; 94.2	95	91	95.8	91.8; 99.8	79	79	100		<0.001
IX. Soft tissue sarcomas	111	93	83.8	76.9; 90.6	129	115	89.1	83.8; 94.5	139	136	97.8	95.4; 99.9	<0.001
X. Germ cell tumours	45	37	82.2	71.1; 93.4	53	51	96.2	91.1; 99.9	57	54	94.7	88.9; 99.9	0.026
XI. Epithelial neoplasms & melanomas	31	11	35.5	18.6; 52.3	65	30	46.2	34.0; 58.3	69	55	79.7	70.2; 89.2	<0.001
XII. Other malignant neoplasms	15	4	26.7	4.3; 49.0	10	5	50.0	19.0; 81.0	5	4	80	44.9; 99.9	0.107

Abbreviations: CI, confidence interval; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, third edition.

^aIncludes the nine clinics of the Swiss Paediatric Oncology Group, ^bp-value derived from Kruskal-Wallis rank sum test for trend, comparing patient numbers treated in paediatric cancer centres between the three time periods.

Supplemental Table 3. Incidence rates of childhood cancer per one million children in Switzerland, other European countries, the USA, Canada, Australia and Korea

<i>Country</i>	Switzerland			Piedmont, Italy	Spain	Sweden	France	Germany	Austria	Western Europe	USA	Canada	Australia	Korea
<i>Period</i>	1985-1994	1995-2004	2005-2014	1967-2011	1982-2002	1990-1998	2000-2004	2005-2014	2009-2011	2001-2010	2000-2013	2006-2010	1997-2006	1999-2011
<i>First author, year of publication</i>	Sommer, 2018			Isaevska, 2017	Peris- Bonet, 2010	Dreifaldt, 2004	Lacour, 2010	Kaatsch, 2014	Karim-Kos, 2016	Steliarova- Foucher, 2017	US Cancer Statistics, 2016	Statistics Canada, 2015	Baade, 2010	Park, 2016
All cancers	143	154	162	157	156	173	157	167	169	n.i.	167	161	158	135
<i>ICCC-3 Main diagnostic groups</i>														
I. Leukaemias	49	47	55	51	46	51	46	57	54	51	54	52	53	46
II. Lymphomas	17	18	18	19	18	19	17	16	14	16	17	18	15	13
III. CNS tumours	28	35	37	37	33	49	36	40	44	38	35	31	36	18
IV. Neuroblastoma	12	10	11	12	15	11	15	14	12	13	13	13	10	12
V. Retinoblastoma	4	5	4	4	5	5	5	4	5	5	5	n.i.	4	5
VI. Renal tumours	9	8	8	7	8	10	10	10	9	10	10	n.i.	9	6
VII. Hepatic tumours	2	2	1	2	2	3	1	2	1	2	3	n.i.	3	3
VIII. Bone tumours	6	8	7	9	8	5	7	6	10	7	6	n.i.	7	7
IX. Soft tissue sarcomas	9	11	12	9	10	8	10	10	10	10	11	10	8	7
X. Germ cell tumours	4	4	5	4	4	5	6	5	5	5	5	5	6	10
XI. Other epithelial neoplasms	3	5	6	4	6	4	4	n.i.	7	4	6	n.i.	7	5
XII. Other malignant neoplasms	1	1	0.4	0.8	0.5	5	0.3	0.2	0	0.3	0.7	n.i.	0.4	3

Abbreviations: CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, third edition; n.i., not indicated.

Supplemental Table 4a. Average annual percentage change (95% CI) of childhood cancer in Switzerland, other European countries, the USA, Canada, Australia, Korea and China

<i>Country</i>	Switzerland	Sweden	Great Britain	Piedmont, Italy	Spain	Western Germany	Eastern Germany	Austria	Ireland
<i>Period</i>	1985-2014	1960-1998	1966-2005	1976-2011	1983-2002	1987-2004	1991-2004	1994-2011	1994-2011
<i>First author, year of publication</i>	Sommer, 2018	Dreifaldt, 2004	Kroll, 2012	Isaevska, 2017	Peris-Bonet, 2010	Spix, 2008	Spix, 2008	Karim-Kos, 2016	National Cancer Registry Ireland, 2014
All cancers	0.7 (0.5; 1.0)	1.0 (0.8; 1.2)	1.0 (0.9; 1.1)	1.1 (0.8; 1.5)	1.9 (1.5; 2.4)	0.8 (0.6; 1.1)	2.1 (1.2; 2.9)	0.7 (-0.2; 1.7)	Girls: 0.8 (-0.2; 1.8) Boys: 0.6 (-0.8; 2.0)
I. Leukaemias	0.8 (0.2; 1.4)	0.9 (0.4; 1.3)	0.7 (0.6; 0.9)	0.6 (0.0; 1.2)	ALL and AML combined: 1.6 (0.8; 2.3)	0.6 (0.2; 1.1)	2.1 (0.7; 3.5)	0.3 (-0.8; 1.4)	0.7 (-1.0; 2.4)
II. Lymphomas	0.0 (-0.9; 1.0)	1.9 (1.2; 2.6)	0.8 (0.6; 1.1)	1976-2007: 1.7 (0.6; 2.7) 2007-2011: -12.2 (-33.2; 15.4)		0.9 (0.2; 1.6)	-0.9 (-3.0; 1.2)	-0.7 (-2.2; 0.8)	-1.3 (-3.8; 1.3)
III. CNS tumours	1985-2002: 3.0 (1.3; 4.6) 2000-2014: -0.2 (-2.4; 2.1)	1.5 (1.0; 1.9)	1.3 (1.2; 1.5)	1.8 (0.9; 2.7)		1.1 (0.6; 1.6)	5.5 (4.6; 7.4)	2.9 (0.9; 5.0)	1994; 1999: -6.3 (-12.9; 0.7) 1999; 2011: 2.7 (0.7; 4.7)
IV. Neuroblastoma	-0.5 (-1.7; 0.7)	1.6 (0.8; 2.4)	0.6 (0.4; 0.9)	1.2 (0.2; 2.1)	n.i.	0.1 (-1.6; 1.8)	2.3 (-0.8; 5.5)	-4.1 (-9.8; 1.6)	n.i.
V. Retinoblastoma	-0.9 (-3.0; 1.2)	0.3 (-1.2; 1.7)	0.6 (0.2; 1.1)	0.7 (-11.1; 14.2)	n.i.	-0.8 (-2.5; 1.0)	n.a.	n.a.	n.i.
VI. Renal tumours	-0.3 (-1.5; 0.9)	0.3 (-0.5; 1.1)	0.7 (0.4; 1.0)	0.2 (-1.1; 1.5)	n.i.	0.6 (-0.4; 1.6)	1.8 (-1.5; 5.2)	0.7 (-2.3; 3.7)	n.i.
VII. Hepatic tumours	n.a.	2.6 (2.0; 3.2)	2.5 (1.7; 3.3)	3.8 (-13.4; 24.4)	n.i.	1.5 (-0.9; 3.9)	n.a.	n.a.	n.i.
VIII. Bone tumours	0.2 (-0.9; 1.4)	0.2 (-0.8; 1.3)	0.5 (0.2; 0.9)	0.0 (-4.1; 4.4)	n.i.	-0.1 (-1.3; 1.0)	0.6 (-2.9; 4.3)	-0.2 (-3.3; 2.8)	n.i.
IX. Soft tissue sarcomas	1.0 (-0.4; 2.5)	0.1 (-0.8; 1.0)	1.6 (1.3; 1.9)	0.5 (-0.7; 1.7)	n.i.	1.3 (0.3; 2.3)	-0.6 (-3.7; 2.6)	0.6 (-1.9; 3.0)	n.i.
X. Germ cell tumours	1.6 (-0.2; 3.4)	1.2 (0.2; 2.2)	1.1 (0.6; 1.6)	2.4 (-5.9; 11.5)	n.i.	-0.2 (-1.5; 1.1)	-1.1 (-5.6; 3.5)	2.4 (-2.3; 7.0)	n.i.
XI. Epithelial neoplasms & melanomas	3.8 (1.7; 6.0)	0.0 (-1.1; 1.1)	1.8 (1.3; 2.3)	3.9 (-1.4; 9.5)	n.i.	2.0 (-0.7; 4.8)	n.a.	n.a.	n.i.
XII. Other malignant neoplasms	n.a.	0.4 (0.01; 0.9)	2.2 (1.2; 3.2)	n.a.	n.i.	n.a.	n.a.	n.a.	n.i.

Supplemental Table 4b (continued). Average annual percentage change (95% CI) of childhood cancer in Switzerland, other European countries, the USA, Canada, Australia, Korea and China

<i>Country</i>	USA	USA	USA	Canada	Australia	Korea	China
<i>Period</i>	1975-2002	1992-2004	2001-2009	1992-2006	1997-2006	1999-2011	2000-2010
<i>First author, year of publication</i>	Ward, 2006	Linabery, 2006	Siegel, 2014	Mitra, 2012	Baade, 2010	Park, 2016	Zheng, 2015
All cancers	0.7*	0.4 (-0.1; 0.8)	0.3 (-0.1; 0.7)	0.0 (-0.5; 0.4)	1983-1994: 1.7 (0.9; 2.5) 1994-2006: -0.1 (-0.7; 0.6)	2.4 (2.1; 2.7)	2.8 (1.1; 4.6)
I. Leukaemias	0.7*	0.7 (-0.1; 1.5)	0.5 (-0.3; 1.3)	1992-1999: 2.4 (0.0; 4.9) 1999-2002: -4.4 (-20.1; 14.2) 2002-2006: -3.0 (-2.6; 9.0)	0.9 (0.3; 1.5)	increase [‡]	n.i.
II. Lymphomas	-0.5*	stable [‡]	0.5 (-0.2; 1.3)	0.0 (-1.4; 1.4)	0.7 (0.0; 1.3)	increase [‡]	n.i.
III. CNS tumours	1.2*	-0.1 (-1.1; 1.0)	-0.1 (-1.0; 0.8)	-0.4 (-1.3; 0.5)	1983-1998: 1.7 (0.6; 2.8) 1998-2006: -1.8 (-4.5; 1.0)	stable [‡]	n.i.
IV. Neuroblastoma	0.5	-0.6 (-2.9; 1.7)	-1.2 (-3.0; 0.8)	-0.2 (-1.8; 1.5)	0.2 (-1.1; 1.4)	5.6*	n.i.
V. Retinoblastoma	0.5	0.3 (-1.5; 2.1)	-0.2 (-1.8; 1.5)	-2.6 (-4.7; -0.4)	0.2 (-1.1; 1.4)	stable [‡]	n.i.
VI. Renal tumours	0.4	-2.1 (-4.6; 0.4)	0.5 (-0.3; 1.3)	-1.3 (-3.2; 0.7)	0.4 (-0.7; 1.6)	stable [‡]	n.i.
VII. Hepatic tumours	2.0*	4.3 (0.2; 8.7)	1.7 (-1.7; 5.3)	1.6 (-0.8; 4.0)	3.3 (0.8; 5.9)	stable [‡]	n.i.
VIII. Bone tumours	0.3	0.2 (-1.4; 1.8)	-0.6 (-1.3; 0.2)	-1.2 (-2.8; 0.5)	0.3 (-0.8; 1.3)	stable [‡]	n.i.
IX. Soft tissue sarcomas	1.0*	stable [‡]	0.3 (-1.4; 1.0)	-1.4 (-3.6; 0.8)	-0.2 (-1.4; 1.1)	increase[‡]	n.i.
X. Germ cell tumours	n.i.	0.8 (-0.7; 0.3)	0.7 (-0.5; 2.0)	-0.4 (-2.2; 1.4)	2.3 (0.9; 3.7)	stable [‡]	n.i.
XI. Epithelial neoplasms & melanomas	n.i.	2.8 (0.5; 5.1)	0.8 (0.1; 1.5)	2.5 (-0.5; 5.6)	1983-1994: 4.3 (1.6; 7.0) 1996-2006: -5.7 (-9.1; -2.2)	5.6*	n.i.
XII. Other malignant neoplasms	n.i.	n.i.	0.6 (-2.9; 4.3)	4.6 (0.1; 9.4)	n.i.	-7.4 (-12.2; -2.3)	n.i.

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, third edition; n.a., not applicable; n.i., not indicated. * p-value>0.05 (no CI reported); [‡] no total values reported. Bold letters highlight AAPCs whose 95% CIs does not include the null value, or whose p-values<0.05.

This table does not contain an exhaustive list of all existing reports and studies on incidence trends of childhood cancer. It includes studies and reports who investigate either all childhood cancer diagnoses combined or both childhood leukaemias and CNS tumours.